November 7, 2002

Edward W. Kordoski, MBA, Ph.D.
Executive Director
Chlorobenzene Producers Association
1850 M Street NW
Washington, DC 20036-5810

Dear Dr. Kordoski:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Chlorobenzenes category posted on the ChemRTK HPV Challenge Program Web site on April 2, 2002. I commend the Chlorobenzene Producers Association for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Chlorobenzene Producers Association advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Chlorobenzenes Category

SUMMARY OF EPA COMMENTS

The sponsor, the SOCMA Chlorobenzene Producers Association, submitted a test plan and robust summaries for the chlorobenzenes chemical category to EPA on March 14, 2002. EPA posted the submission on the Chemical RTK HPV Challenge Web site on April 2, 2002. The category members include mono-, di-, and trichlorobenzenes. Supporting data on two analogs are also included in the submission.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitter's support for grouping the chemicals under this category is appropriate.

2. Physicochemical Properties and Environmental Fate. Adequate data are available for all endpoints for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

3. Health Effects. Adequate data are available for all endpoints for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

4. Ecological Effects. Although the fish and aquatic invertebrate studies on monochlorobenzene are inadequate, EPA considers that these endpoints can be adequately addressed for the category by providing SAR data on monochlorobenzene and by reading across from adequate data on the other category members. EPA considers that the algal toxicity endpoint has been adequately addressed for the purposes of the HPV Challenge Program; however, the submitter needs to enhance the robust summaries for algae studies by providing the missing data elements on test conditions.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission

EPA COMMENTS ON THE CHLOROBENZENES CATEGORY CHALLENGE SUBMISSION

Category Definition

The category includes the following members: monochlorobenzene (CAS No. 108-90-7), 1,2-dichlorobenzene (CAS No. 95-50-1), 1,3-dichlorobenzene (CAS No. 541-73-1), and 1,2,3-trichlorobenzene (CAS No. 87-61-6). 1,4-Dichlorobenzene (CAS No. 106-46-7) and 1,2,4-trichlorobenzene (CAS No. 120-82-1) were submitted as structurally-related analogs. The six substances differ only in the number and positions of the chlorine substituents. The category definition is clear and unambiguous.

Category Justification

The test plan provides tabular documentation of the close similarity of the category members and analogs in physicochemical properties, environmental fate parameters, health effects and ecotoxicity endpoints. These similarities and the closely related structures support using analog data to address the unfilled endpoints for the category members.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient, water solubility)

The data for all endpoints are adequate for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data for all endpoints are adequate for the purposes of the HPV Challenge Program.

Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate data are available for all endpoints for the purposes of the HPV Challenge Program. The following comments pertain to the submitter's conclusions in the text of the test plan.

Reproductive Toxicity. The submitter concluded that the chemicals in this catergory are not reproductive toxicants. Although EPA agrees that no effects on mating or fertility were seen and that a low incidence of microscopic lesions of the testes did not affect reproductive performance, decreased pup survival and decreased pup body weights were seen in the study with 1,2-dichlorobenzene and were confirmed in a 2-generation study with the analog chemical 1,4-dichlorobenzene. While these endpoints are noted in Table 9 of the test plan, the text is limited to the statement that these chemicals "...have no effect on fertility and are not toxic to reproductive organs..." which is misleading because offspring survival is definitely a measure of reproductive ability.

Developmental Toxicity. The submitter repeated the study authors' conclusions in the test plan that chemicals in this category are not teratogenic and therefore not fetotoxic at the doses tested. However, effects were seen in fetuses that included skeletal variations in rats and an increased incidence of retro-esophageal right subclavian artery in rabbits. EPA believes that skeletal variations are clearly indicative of fetotoxicity, albeit mild, and disagrees with the conclusions in the test plan. In addition, describing these effects in one sentence followed by the conclusion that these chemicals are not teratogenic is contradictory. The test plan should be reworded to state that while major malformations were not induced in any study, skeletal and soft tissue variations were increased at doses that also resulted in mild maternal toxicity.

NOTE: Both rat and rabbit entries for monochlorobenzene (John et al., 1984) in Table 10 of the test plan are footnoted stating "Assigned a reliability rating of 4 and the data came from an abstract". This is incorrect because robust summaries for these studies assigned a reliability code of 1 and they appear to be well-conducted studies. Discrepancies also exist between Table 10 in the test plan and the robust summary for the NOAELs given for the studies with 1,4-dichlorobenzene in rabbits and 1,2,3-trichlorobenzene in rats. EPA believes that both entries in the test plan are correct.

Ecological Effects (fish, invertebrates, algal toxicity)

The submitter needs to provide an SAR prediction for the 96-hour monochlorobenzene fish study to help interpret the volatility problem encountered during the study. EPA believes that it will also support the read-across approach. Although the submitter provided 24-hour acute toxicity daphnia data for several chemicals, rather than the required 48-hour data, EPA believes that this endpoint can be adequately addressed by a read-across approach. EPA suggests that the submitter provide the SAR prediction for this endpoint to support the submitted data and for read-across purposes. The submitted SAR data should be in robust summary format with all input values included.

Specific Comments on the Robust Summaries

Physicochemical Properties

CAS # 108-90-7: The submitter needs to provide information on the method used for measuring vapor pressure and water solubility, or indicate if the data were calculated.

CAS # 95-50-1: The submitter needs to provide information on the method used for measuring melting point, boiling point, vapor pressure, octanol/water partition coefficient, and water solubility, or indicate if the data were calculated.

CAS # 541-73-1, and CAS # 87-61-6: The submitter needs to provide information on the method used for measuring melting point, boiling point, vapor pressure, and water solubility, or indicate if the data were calculated.

Environmental Fate

Biodegradation. CAS # 541-73-1: In the robust summary (Section 3.5, page 13 / 58), under the heading of "Test substance," the submitter wrote "no data." The submitter needs to provide adequate identification of the test substance.

Fugacity. The submitter needs to provide model input values used in all fugacity calculations.

Health Effects

The following deficiencies were seen in summaries that were identified as critical studies by the submitter.

Acute Toxicity.

Monochlorobenzene: Only 2-3 males and females per group were tested; study design and statistical methods used were not included.

1,2-dichlorobenzene: The number of animals tested and the exposure time did not conform to the guidelines; the study design was not described, and statistical methods were not included.

1,3-dichlorobenzene: The purity of the test material and statistical methods were not reported.

Developmental Toxicity. The statement that the results show no evidence of teratogenic effects and are therefore not fetotoxic should be deleted or rewritten to more accurately describe the results. The study in which rabbits were exposed to monochlorobenzene should be identified as a key study.

Ecological Effects

Algae. Deviations from the AAPBT method should be described, and the submitter should provide the following additional information: purity of test substance, control response in terms of the increase in cell concentration within the three day period, and the pH, dissolved oxygen, and temperature readings throughout the test.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.